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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/383,978	08/26/99	SCHALLER H	BBI-102CP

EXAMINER	
NGUYEN, D	

ART UNIT	PAPER NUMBER
1632	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/383,978	SCHALLER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on November 21, 2000 for a Continued Prosecution Application (CPA) under 37 C.F.R. 1.53(d) based on the same Application No. 09/383978 is acceptable and a CPA has been established. Claims 1-40 are pending in this application. An action on the CPA follows:

Claim Objections

Claim 11 is objected to because of the following informalities: A period is needed at the end of the claim. Appropriate correction is required.

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. A cytokine is a modulating agent, therefore every embodiment in claim 30 is already present in the independent claim 23.

Claim 35 is objected to because of the following informalities: Misspelled IFNα in the claim. Appropriate correction is required.

Claim R jections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 9-32 are directed to a method of treating a subject with a hepatic disorder or a hepatitis infection comprising: providing replication defective hepadnavirus particles at a titre level competent to infect hepatocytes of the subject with the hepatic disorder or with hepatitis, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with a therapeutic gene, preferably a gene encoding a cytokine, such that expression of the therapeutic gene is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes of the subject with the hepadnavirus particles such that the therapeutic gene is delivered into the hepatocytes and expressed in the hepatocytes at a level sufficient to treat the hepatic disorder or the hepatitis. Claims 33-38 are directed to a replication defective hepadnavirus particle whose genome

comprises a therapeutic gene operably linked to regulatory sequences of the preS or S-gene, a pharmaceutical composition comprising the same with a pharmaceutical acceptable carrier or with a helper virus. Claims 39-40 are drawn to a method of producing therapeutic replication defective hepadnavirus particles at a titre level suitable for therapeutic use.

The specification teaches the preparation and production of recombinant replication defective duck and human hepatitis B virus (rDHBV and rHBV, respectively) stocks. The specification further discloses that an efficient transfer and stable expression of the marker GFP gene operably linked to DHBV S-promoter could be established for viable cultured hepatocytes. In addition, the delivery of a transgene mediated by rDHBV has been shown to be both hepatocyte and species-specific as shown by the lack of GFP expression in non-parenchymal cells, primarily sinusoidal endothelial cells and Kupffer cells constituting about 15% of the total cell population in the primary hepatocyte cultures, and in primary mouse hepatocytes. Moreover, intravenous injection of rDHBV-GFP in ducklings resulted in the recovery of GFP-fluorescent hepatocytes 7 days post infection, indicating a successful *in vivo* gene transfer mediated by rDHBV-GFP. The specification further teaches that rDHBV can superinfect DHPV-infected hepatocytes, even though the transduction efficiency is 20-fold lower than the one observed with hepatocyte cultures not preinfected with DHBV. Additionally, superinfection of cultured DHPV-infected hepatocytes with rDHBV-IFN resulted in a decrease in DHBV production relative to untreated controls, indicating that the inhibition was caused by the expression of transduced IFN transgene. Similarly,

human rHBV was shown to infect cultured primary human hepatocytes comparable to wild type HBV, and that the delivery of a transgene mediated by rHBV is species and hepatocyte-specific *in vitro*.

The above evidence is noted and considered. However, the evidence can not be extrapolated to the instantly claimed invention which is directed to a method of treating a subject having a hepatic disorder or a hepatitis infection utilizing the replication defective recombinant hepadnavirus particles of the present invention, a pharmaceutical composition comprising the same replication defective recombinant hepadavirus particles and a method for producing the same.

The specification is not enabled for the instantly claimed invention because at the effective filing date of the present application, the art of gene therapy was still considered to be highly unpredictable and immature. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that although significant progress has been achieved in understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, the lack of long term stable transgene expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues (page 474, column 2, lines 4-9 of the last paragraph). Dang et al. further stated that "This work shop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement **to make gene therapy a reality**" (page 471, column 1, last sentence of first paragraph). The instant specification fails to provide sufficient guidance or direction

regarding to the use of the replication defective recombinant hepadnavirus particles comprising a therapeutic gene, a method of producing the same and a method of treatment as claimed for a skilled artisan to achieve any therapeutic effects. The specification fails to provide a nexus between the expression of a marker gene GFP in hepatocytes *in vivo* and therapeutic results hoped to be achieved for treating a subject with a hepatic disorder or with a hepatitis infection with the replication defective recombinant hepadnavirus of the present invention. Since the prior art at the time the invention was made does not provide such teachings, it is incumbent upon the present specification to do so. With respect to the apparent low *in vivo* transduction rates reported in this application (1 GFP-positive cell per 10^4 to 10^5 hepatocytes and at least 20-time less efficient for preinfected hepatocytes), the instant specification fails to demonstrate that any therapeutic results could be achieved at such low transduction rates. Nor does it provide specific teachings for optimizing or improving conditions (dosage used, route of delivery, recombinant vector constructs) to achieve an effective transduction rate in the targeted cells to obtain therapeutic results. Moreover, it is also uncertain how stable is the *in vivo* expression of therapeutic genes in targeted cells to yield therapeutic results. Eck & Wilson (Gene-based therapy, PTO-892 in paper no. 7) noted that factors such as the level of mRNA produced, the stability of the protein generated, the protein's proper compartmentalization within the cell or its secretory fate differ dramatically based on which protein being produced (page 81, column 2 continues to page 82). Therefore, the level of gene expression, its duration and its *in vivo* therapeutic effect sought to achieve are not always predictable or they can be overcome

with routine experimentation. Due to the lack of guidance as outlined above, it would have required undue experimentation without a predictable expectation of success for a skilled artisan to make and use the claimed invention.

With regard to the treatment method claims, they encompass any an all routes of delivery of the replication defective recombinant hepadnavirus particles into a patient having a hepatic disorder or hepatitis infection. Although the specification clearly teaches the recombinant hepadnariviruse particles are species and hepatocyte-specific in primary hepatocyte cultures *in vitro*, it is noted that the specification also discloses that "HBV strains infecting various human organs, including hepatocytes, exocrine and endocrine cells, tubular epithelium of the kidney, spleen cells, leukocytes, lymphocytes, e.g., splenic, peripheral blood, B or T lymphocytes, and cells of the lymph nodes and pancreas" (See page 11, lines 23-28). Given a broad range of human organs and cell types that hepatitis B viruses can infect *in vivo*, and in light of the low transfection rate of the recombinant hepadnavirus particles noted above, it is unclear how an effective level of recombinant hepadnavirus particles can be delivered to targeted cells, for this instance hepatocytes, by any and all means of delivery to achieve therapeutic results. Additionally, adverse host immune responses reactive against administering recombinant hepadnavirus particles may further reduce the effectiveness of transgene delivery to intended targeted cells. Vector targeting *in vivo* continues to be unpredictable and it is a major obstacle for achieving an effective gene delivery to targeted cells and tissues. The instant specification fails to provide sufficient teachings for a skilled artisan how to overcome the aforementioned obstacles in obtaining

therapeutic effects for the claimed treatment methods. With the lack of sufficient guidance or direction provided by the specification, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and use the claimed invention.

Moreover, the nature of the instant claims also falls within the realm of the physiological art. The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictablity of factors involved.

Accordingly, due to the lack of guidance and direction provided by the specification, the amount of experimentation necessary, the unpredictability of the gene therapy and physiological arts, and the breadth of the instant claims, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and **use** the instantly claimed invention.

It is noted that with respect to claims 33-36 and 39, the enablement rejection set forth above can be overcome if the recitation of "therapeutic gene" and "therapeutic replication defective hepadnavirus particles" in respective claims is removed.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing a heterologous gene in hepatocytes *in culture* comprising: providing replication defective hepadnavirus particles at a titer level competent to infect hepatocytes, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with the heterologous gene such that expression of the heterologous gene is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes with the hepadnavirus such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes, does not reasonably provide enablement for the same method *in vivo* as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method for expressing a heterologous gene in hepatocytes comprising: providing replication defective hepadnavirus particles at a titre level competent to infect hepatocytes, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with the heterologous gene such that expression of the heterologous gene is regulated by regulatory sequences of the preS

or S-gene; and infecting hepatocytes with the hepadnavirus such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes.

The claims encompass both *in vitro* and *in vivo* methods for expressing a heterologous gene in hepatocytes. When read in light of the specification, the sole purpose for the *in vivo* method as claimed is for providing an effective level of a therapeutic gene product, preferably a cytokine, more preferably IFNα, TNFα, IFNβ, IL-18 and IFNγ, to treat a subject having a hepatic disorder or hepatitis infection. As enablement requires the specification to teach how to make and **use** the claimed invention, the instant specification fails to enable the use of the broadly claimed method for gene therapy purpose for reasons already set forth in the rejection of claims 9-40 above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 9-32 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 23 and their dependent claims are vague and indefinite in the recitation of "level sufficient to treat" because it is unclear what factors are encompassed in the claims to determine what is sufficient and what is not sufficient to treat hepatic disorder or hepatitis. The metes and bounds of the claims can not be clearly determined.

Claim 39 and its dependent claim are vague and indefinite in the recitation of "level suitable for therapeutic use" because it is unclear what factors are encompassed in the claims to determine what is suitable and what is not suitable level for a therapeutic use. The metes and bounds of the claims can not be clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-2, 4, 6, 33 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Tyrrell et al. (U.S. Patent No. 5,981,274, PTO-1449, B1 in paper no.6).

Claims 1-2, 4 and 6 are directed to a method for expressing a heterologous gene in hepatocytes comprising providing replication defective hepadnavirus particles, preferably human hepatitis B virus particles, at a titer level competent to infect hepatocytes, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with the heterologous gene, preferably one encodes a modulating agent, such that expression of the heterologous gene is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes with the hepadnavirus such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes. Claim 33 is directed to a replication defective hepadnavirus particle, wherein a region of

the preS or S-gene of the hepadnavirus genome has been replaced with a therapeutic gene such that expression of the therapeutic gene is regulated by regulatory sequences of the preS or S-gene. Claim 37 is drawn to a pharmaceutical composition comprising the same replication defective hepadnavirus particle and a pharmaceutically acceptable carrier. With regard to claims 33 and 37, it is noted that for composition claims the intended uses are not given any patentable weight in view of the prior art.

Tyrrell et al. teach the preparation of replication defective recombinant HBV viruses comprising heterologous gene sequences operably linked to the preS1 promoter for the expression of functional heterologous gene products in liver cells (See column 15, lines 31 continues to lines 10 of column 16, and claims 1-3, 9-12). The heterologous gene products encompass those provide therapeutic functions, including those that correct an error in cellular metabolism, to inactivate a pathogen or to kill a cancerous cell (column 11, lines 25-30). Such gene products are considered to be modulating agents. Tyrrell et al. further teach that the replication defective HBV vectors contain a major deletion in the *pol* ORF to permit the insertion of heterologous gene sequences up to about 2.2 kb in length, such that the total genome size of the recombinant HBV vectors is within the packaging limit of the HBV particle (column 15, lines 44-49). It should be noted that the ORF for the *pol* gene overlaps with those of preS1/S2/S genes and partially with X gene (See Fig. 1A). Additionally, Tyrrell et al. disclose that the deletion may also occur within the preS/preS2/S gene sequences and that replication defective recombinant virus genome lacks a functional X and/or S gene or functional preS1/S or preS2/S genes (column 3, lines 5-16). Tyrrell et al. further

teach that the recombinant virus particles are resuspended in phosphate buffered solution (PBS), a pharmaceutically acceptable carrier, prior to infection of HepG2 cells (column 33, lines 1-2). Therefore, Tyrrell et al. clearly anticipate the instant claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5-8, 33-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyrrell et al. (U.S. Patent No. 5,981,274, PTO-1449, B1 in paper no.6) in view of Gutterman (PNAS 91:1198-1205, PTO-1449, B3 in paper no. 6) and Cavanaugh et al. (J. Virology 71:3236-3243, 1997).

Claims 1, 3 and 5-8 are drawn to a method for expressing a heterologous gene in hepatocytes comprising providing replication defective hepadnavirus particles at a titer level competent to infect hepatocytes, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with the heterologous gene such that expression of the heterologous gene is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes with the hepadnavirus such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes; the same method wherein the heterologous gene is inserted into a region of the S-gene such that nucleotides encoding at least one amino acid of the S protein are fused in-framed to the 5'end of the heterologous gene; or wherein the heterologous gene is inserted after the authentic AUG of the S-gene, and the heterologous gene is inserted such that nucleotides encoding at least one amino acid of the S protein are fused in-frame to the 5'end of the heterologous gene; or wherein the heterologous gene encodes a modulating agent, preferably a cytokine, and more preferably IFNα.

Claims 33-36 are directed to a replication defective hepadnavirus particle, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with a therapeutic gene such that expression of the therapeutic gene is regulated by regulatory sequences of the preS or S-gene; the same wherein therapeutic gene is a cytokine, preferably IFNα or it is selected from the group consisting of TNFα, IFNβ, IL-18 and IFNγ. Claim 38 is drawn to a pharmaceutical composition comprising the same replication defective hepadnavirus particle and a helper virus. With regard to claims 33-

36 and 38, it is noted that for composition claims the intended uses are not given any patentable weight in view of the prior art.

Tyrrell et al. teach the preparation of replication defective recombinant HBV viruses comprising heterologous gene sequences operably linked to the preS1 promoter for the expression of functional heterologous gene products in liver cells (See column 15, lines 31 continues to lines 10 of column 16, and claims 1-3, 9-12). The heterologous gene products encompass those provide therapeutic functions, including those that correct an error in cellular metabolism, to inactivate a pathogen or to kill a cancerous cell (column 11, lines 25-30). Such gene products are considered to be modulating agents. Tyrrell et al. further teach that the replication defective HBV vectors contain a major deletion in the *pol* ORF to permit the insertion of heterologous gene sequences up to about 2.2 kb in length, such that the total genome size of the recombinant HBV vectors is within the packaging limit of the HBV particle (column 15, lines 44-49). It should be noted that the ORF for the *pol* gene overlaps with those of preS1/S2/S genes and partially with that of X gene (See Fig. 1A). Additionally, Tyrrell et al. disclose that the deletion may also occur within the preS/preS2/S gene sequences and that replication defective recombinant virus genome lacks a functional X and/or S gene or functional preS1/S or preS2/S genes (column 3, lines 5-16). Tyrrell et al. further teach that the recombinant virus particles are resuspended in phosphate buffered solution (PBS) prior to infection of HepG2 cells (column 33, lines 1-2). However, Tyrell et al. do not specifically teach the preparation of replication defective recombinant HBV viruses comprising a therapeutic gene encoding for a cytokine (IFNα,

TNFα, IFNβ, IL-18 or IFNγ), a method for expressing a heterologous gene in hepatocytes using the same viruses, or the same method wherein the heterologous gene is inserted into a region of the S-gene with recited limitations, or a composition comprising the replication defective hepadnavirus particle and a helper virus.

Gutterman teach that IFNα is the treatment of choice for patients with chronic HBV and hepatitis C virus infections (page 1201, column 3, last sentence; and columns 1 and 2 of page 1202). Cavanaugh et al. disclose that HBV-specific cytotoxic T lymphocytes inhibit HBV replication in the livers of transgenic mice by a noncytolytic process that is mediated in part by IFN-γ, and the same antiviral response can be initiated by recombinant IL-12 via its primarily induction of IFN-γ production (See abstract). In addition, it is already known in the art that IFN-γ, TNFα, and IFNα/β can inhibit HBV gene expression by a post-translational process that destabilizes the viral RNA in the nucleus of the cell and accelerates its degradation (Cavanaugh et al., page 3242, column 1, lines 8-20).

Accordingly, at the time of the instant invention it would have been obvious to an ordinary skilled artisan to insert heterologous genes encoding for IFNα, IFN-γ, TNFα, into the replication defective recombinant hepadnavirus particles disclosed by Tyrrell et al. An ordinary skilled artisan would have been motivated to make this modification because these therapeutic gene products have been shown to inhibit HBV replication and/or HBV gene expression, particularly IFNα has been approved for treating patients with chronic HBV and hepatitis C virus infections as taught by Gutterman and Cavanaugh et al. In addition, cDNAs encoding the aforementioned therapeutic gene

products are readily available in the art at the effective filing date of the present application. Moreover, Tyrrell et al. also contemplate the use of a heterologous gene product that inactivates a pathogen such as hepatitis virus (column 11, lines 25-28). Although Tyrrell et al. merely disclose that heterologous gene sequences can be inserted within the preS/preS2/S gene sequences and that replication defective recombinant virus genome lacks a functional X and/or S gene or functional preS1/S or preS2/S genes (column 3, lines 5-16), it would have been obvious and within the scope of skills of an ordinary skilled artisan at the effective time of the present invention that the insertion of such heterologous gene sequences would have been fused in frame with the nucleotides encoding at least one amino acid of the S protein and/or after the authentic AUG of the S gene for expressing the heterologous gene sequences, should the insertion is made within the S gene sequence. Additionally, a composition comprising the replication defective hepadnavirus particle of the instant invention and a helper virus would also be obvious because Tyrrell et al. teach the use of a plasmid capable of providing in trans hepatitis B virus gene products sufficient to complement the recombinant viral genome lacking the ability to produce at least one viral product required for packaging to produce viral particles (column 3, first full paragraph and claims 17-25). A helper virus producing messenger RNAs capable of supplying functions required in trans for packaging can be substituted for said plasmid, and such helper virus is available in the art at the time of the instant invention.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

It is noted that the reference of Tyrrell et al. contains teachings related to an embodiment of claim 39 (See claims 17-29 in Patent No. 5,981,274). In addition, the reference of Chaisomchit et al. (Gene therapy 4:1330-1340, 1997; AB, PTO-1449 in paper no. 4) contains parts of the same teachings disclosed by Tyrell et al.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Deborah Crouch, Ph.D., may be reached at (703) 308-1126, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Deborah Crouch

Quang Nguyen, Ph.D.
Examiner, AU 1632

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630